# Cystic Fibrosis in Europe - remote measurement of outcome

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**Summary**: Childhood Cystic Fibrosis (CF) occurs randomly across all European social strata enabling unbiased sampling of CF health care provision. Through an FP6 programme, EuroCareCF, www.eurocarecf.eu, we developed a 35-country European CF demographic registry (McCormick et al 2010) to compare CF outcomes; applying standards shown at www.cystic-fibrosis.org.uk previously used to create a country-specific registry. Implementing this standard, we collated demographic/genotype data from ~30,000 CF patients scattered from Iceland to the Black Sea. This work was underpinned by patient consent backed by legal opinion and complied with ethical and data management legislation. In our CF Registry, a widely different country-specific prevalence of childhood CF exists despite both a similar heterozygote CF gene frequency and population size between Eastern and Western Europe. In particular, during Eastern (but not Western) European childhood, we observe a significant paucity of the homozygous F508-del form of CF that should be diagnosed in childhood in over 90% of presentations in Western Europe i.e. this potentially lethal phenotype should be highly prevalent had healthcare in babyhood been appropriate for CF children. Our failure to find sufficient CF-affected children suggests that an excess premature CF mortality exists in parts of Eastern Europe which has largely disappeared in better resourced Western Europe that now has a vanishingly low mortality (<5%) for the severe commonly occurring F508del homozygous CF during childhood. The reasons for this health care gap require investigation by governments. Our demographic approach (see web appendices in McCormick et al 2010) and findings may also be of interest to other rare disease therapists. Supported by the Sixth Framework Programme for Research, priority 1 "Life Sciences, Genomics and Biotechnology for Health" LSHM-CT-2005-018932 and MZOFNM2005 to MM. We thank the European CF Society Registry Steering Group for collaboration and support. **McCormick et al The Lancet 2010; 375:1007-1013.**

## Introduction

•Cystic Fibrosis (CF) is a randomly occurring genetic condition which is one of the commonest life-limiting autosomal recessive conditions in Europe
•CF Disease Registries have grown in size, coverage and sophistication since the 1960s
•Previous international disease comparisons have been limited by conflicting systems of data collection and data definitions
•Through an FP6 programme, Eurocare CF, we developed a 35 country European CF demographic registry to compare disease outcomes

## Methods

•The registry was a collaboration between EuroCareCF and The European CF Society
•35 countries were enrolled across the European geographical area
•Core data on age, age at diagnosis, genotype and gender were collected
•Data was collected between January 2003 and December 2007
•Europe was divided by European Union membership in 2003 to reflect the era present for most of the patient's lives
•We modelled the age profile of EU patients on non-EU countries to estimate the size of the CF population in non-EU countries and compare it with the observed size

| | EU countries | Non-EU countries | p value |
|---|---|---|---|
| Age (years)* | 17·0 (9·5–25·6); 18·5 (11·5) | 12·1 (6·0–19·2); 13·7 (9·9) | <0·0001 |
| <5 | 2823 (11%) | 786 (21%) | – |
| <18 | 13 472 (53%) | 2732 (72%) | – |
| 18–40 | 10 519 (42%) | 1001 (26%) | – |
| >40 | 1205 (5%) | 76 (2%) | – |
| Age at diagnosis (years)* | 0·5 (0·1–2·8); 3·4 (7·4) | 0·9 (0·3–4·3); 3·9 (7·1) | <0·0001 |
| Age of patients with homozygous Phe508del (years)† | 16·5 (9·4–24·3); 17·7 (10·5) | 11·4 (5·5–17·8); 12·4 (8·1) | <0·0001 |
| <5 | 1197 (11%) | 216 (22%) | – |
| <18 | 6043 (56%) | 735 (76%) | – |
| 18–40 | 4494 (41%) | 230 (24%) | – |
| >40 | 341 (3%) | 3 (<1%) | – |

Data are median (IQR), mean (SD), or number (%). –=data not calculated. *Recorded for 25 216 patients in countries with and 3806 in countries without EU membership. †Recorded for 22 856 patients in countries with and 3028 in countries without EU membership. Site coded for 10 878 patients in countries with and 958 in countries without EU membership.

**Table: Demographic indicators of cystic fibrosis populations in EU and non-EU countries**

## Results

•29025 CF patients (25216 EU patients, 3809 non-EU patients) from 35 countries
•The population increased to a peak in the age-group of 10–14 years, with less than 2% of the population older than 45 years (figure 1)
•Median age was 16·3 years (IQR 8·9–24·8) and mean age was 17·9 years (SD 11·4), with an age range of 15·7–20·5 years in EU countries versus 6·1–23·0 years in non-EU countries (table)
•Median age in EU countries was 4·9 years older than in non-EU countries (95% CI 4·4–5·1)
•Proportions of patients in the older age-groups were smaller in non-EU than in EU countries even before the age of 20 years, with striking differences in the proportions of patients aged 35–44 years (figure 2A)
•In EU countries, between the age-groups of 0–9 years and 10–19 years, the number of patients with CF increased by 24%, whereas the number of patients decreased by more than 10% in non-EU countries (figure 2B)
•Population size decreased at a younger age and more sharply in non-EU countries than in EU countries, with the change in population size differing by 20–30% between EU and non-EU countries for patients aged 0–40 years
•Only 21 (60%) of the 35 countries had patients older than 40 years (one in 21 patients in EU countries *vs* one in 50 in non-EU countries), and such patients were more likely to live in EU than in non-EU countries (OR 2·4, 95% CI 1·9–3·0, p<0·0001)
•The differences between EU and non-EU countries shown in figure 2A persist even after exclusion of milder genotypes (figure 3A), and, despite a common severe genotype, the population declines at an earlier age and with greater rapidity in non-EU countries than in EU countries (figure 3B)
•This exclude the possibility that the differences between EU and non- EU countries could be caused by a higher proportion of milder genotypes in EU countries
•Patients with homozygous Phe508del had an age range of 0·1–60·8 years in EU countries versus 0·1–49·5 years in non-EU countries
•We modelled demographic indicators of EU countries on non-EU countries to estimate the size of the CF population, which showed that a further 3212 patients—84% more than we recorded from data registries—would be alive in non-EU countries if the EU demographic conditions had applied (figure 4).
•Notably, the main driver for this difference is the age profile for patients aged older than 10 years. Conversely, had the CF population in EU countries of 25216 patients been exposed to the demographic conditions of non-EU countries, we calculated that the population would be 54% of the original size with 13680 patients (loss of 11536 patients; data not shown)

## •Discussion

•Far fewer children and young adults have CF in non-EU countries than expected; poor survival in non-EU countries could be a contributing factor
•This disparity in demographic indicators might be due to reduced availability of specialist drugs, equipment, and trained multidisciplinary staff in non-EU countries, rather than lower gene frequency, greater disease severity, or poorer treatment adherence than in EU countries
•Equitable investment in the basic provision of CF care to new EU and non-EU nations alike could yield the greatest health and cost benefits
•An extra US$7·8 million per year (£4·9 million) at 2002 prices would be needed to care for the additional 3212 patients that we predicted would be alive in non-EU countries if these patients had the demographic indicators of EU countries
•These data and methodology will be of interest to governments, CF organisations providing funding for care and rare disease therapists

## References

McCormick J et al. Comparative demographics of the European cystic fibrosis population: a cross-sectional database analysis. The Lancet 2010; 375: 1007 - 1013

**Acknowledgments**
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## Key Messages

Earlier mortality and differences in access to care and medicines are likely to be responsible for the stark survival differences seen amongst ~30,000 CF patients between European Union and (EU) and non-EU countries in this 35 country Registry project.

1

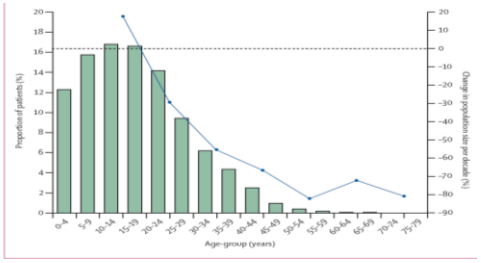
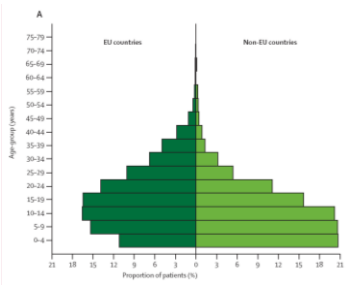
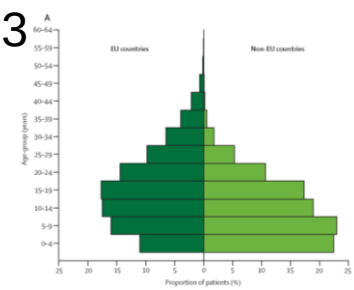



***Figure 1:*** **Age distribution of patients with cystic fibrosis in Europe (green bars) and percentage change in the size of the cystic fibrosis population from the previous 10-year age-group (blue line)**
Black dashed line indicates zero change in population size. Datapoints for percentage change in population size are positioned at the midpoint of the decade that they represent.

2




3



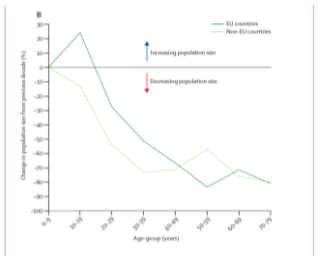




***Figure 2:*** **Population pyramid of mean age of patients with cystic fibrosis in EU and non-EU countries (A), and percentage change in the size of the cystic fibrosis population from the previous 10-year age-group (B)**

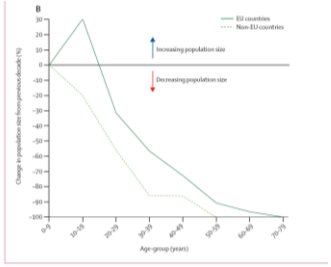



***Figure 3:*** **Population pyramid of mean age of patients with cystic fibrosis and homozygous Phe508del in EU and non-EU countries (A) and percentage change in the size of the cystic fibrosis population with homozygous Phe508del from the previous 10-year age-group (B)**

4

**Setting a target for CF outcomes - a virtual approach**

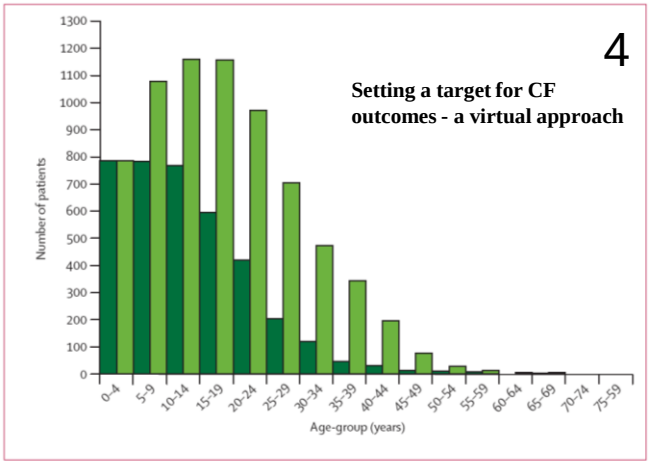



***Figure 4:*** **Size of the cystic fibrosis population in non-EU countries recorded from data registries (dark green bars) and remodelled with demographic indicators from EU countries (light green bars)**